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CMF + Radiotherapy in the Primary Treatment of Operable Breast Cancer: Preliminary Results of a Phase II Pilot Study

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Background and Objectives: Chemotherapy and radiotherapy have been investigated in several studies about their role in primary (neoadjuvant) treatment before surgery in breast cancer. We proposed a pilot study to evaluate a primary scheme of alternate radio-chemotherapy in the treatment of operable (T2- small T3) breast cancer.
Methods: 14 patients were recruited. Cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) were administered on days 1 and 8, every 4 wk, for two cycles. Radiotherapy was administered during the 3rd and 4th wk (5 d/wk) after the beginning of chemotherapy. The patients were operated on within 2–4 wk. All the patients received four additional cycles of chemotherapy within 1 mo after surgery.
Results: We observed: 1 (8.3%) complete remission (CR), 8 (66.7%) partial remission (PR), 3 (25%) stationary disease (SD); no progressive disease was observed. Modified radical mastectomy was performed on 7 patients (58.3%). Conservative surgery was performed on 5 cases (41.7%). No major complications were observed. No patient has shown local or distant recurrence.
Conclusions: This study shows the feasibility of a primary chemo-radiotherapy treatment for breast cancer. But to evaluate the impact of this therapy on overall survival and recurrence risk and its possible introduction in clinical practice, we need larger series and longer follow-up.
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Key Words: breast cancer; neoadjuvant therapy; radiotherapy; chemotherapy

INTRODUCTION

The aim of neoadjuvant chemotherapy is to decrease the size of primary tumors and reduce the systemic dissemination of micrometastatic disease, before appropriate surgical treatment. This should lead to improved local control of the disease as well as improved survival. At over 20 yr since the early experiences of Fisher and Bonadonna, the adjuvant therapy of breast cancer is still under investigation. In fact the metanalysis of all randomized trials underlined that up to now no treatment can be considered ideal [1,2]. Administration of adjuvant systemic chemotherapy already during surgery in patients with operable tumors or preoperatively, as primary therapy, is being evaluated [3].

Recently, interest in the integration of chemotherapy and radiotherapy has grown. It has been proven that both radiotherapy and chemotherapy lead to the death of stem cells in normal tissue as well as in rapidly proliferating tissue [3,4]. Moreover, an enhancement of the cytotoxic

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effect through the simultaneous application of the two therapies has been suggested [5].

In this research field, the Gruppo di Ricerca sulla Ormono-Chemio Terapia Adiuvante (G.R.O.C.T.A., Adjuvant Hormono-Chemotherapy Research Group) proposed a pilot study in order to evaluate feasibility, efficacy, and therapeutic effect of a primary chemo-radiotherapy scheme in the treatment of operable breast cancer.

MATERIALS AND METHODS

The participating departments recruited 48 patients. Fourteen of them were observed and selected in the Department of Surgery, Division of Endocrine Surgery, in collaboration with the Department of Radiotherapy, of the Catholic School of Medicine in Rome.

Eligibility criteria were: cytological and/or histologic diagnosis of breast cancer; tumor size between 2.5 and 6 cm or not allowing conservative treatment; good performance status; age < 70 yr; no distant metastasis; normal hematological, renal, and hepatic functions; fully informed consent.

Before treatment, all the patients were accurately evaluated by physical examination, complete blood count, complete hematochemical tests, specific markers, chest X-ray, electrocardiography, mammogram, breast ultrasonography, fine-needle aspiration biopsy and/or tru-cut biopsy, bone scan, and hepatic ultrasonography.

Recruited patients were submitted to a preoperative chemo-radiotherapy treatment. CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) was administered intravenously (i.v.) on d 1 and 8, every 4 wk, for two cycles. Radiotherapy (cobalt therapy or linear accelerator) was administered during the 3rd and 4th wk (5 d/wk) after the beginning of chemotherapy, with two fractions of 1.8 Gy every day (total dose: 36 Gy).

After treatment, the patients were reevaluated by physical examination, mammogram, and ultrasound. The patients were operated on within 2–4 weeks. After surgery, all patients received four additional cycles of chemotherapy (CMF if node negative; epidoxorubicin and cyclophosphamide if node positive) within 1 month after surgery.

RESULTS

The patients were aged between 31 and 66 yr (average 53 yr). Six patients out of 14 (42.9%) were premenopausal. At clinical examination, tumor size was between 2.5 and 9 cm (average: 4.2 cm); at mammogram and/or ultrasound, tumor size was between 2.5 and 6 cm (average: 3.75 cm). Six patients out of 14 (42.9%) presented clinically with nodal metastases. After preoperative treatment, we observed: 1/14 (7.1%) complete remission (CR), 10/14 (71.5%) partial remissions (PR), 3/14 (21.4%) stationary disease (SD); no progressive disease (PD) was observed. The percentage of pathological overall remission was 78.6% (11 cases out of 14). Chemo-radiotherapy complications were: 1/14 (7.1%) pancytopenia, (which required a short suspension of the treatment), 1/14 (7.1%) leukopenia, and 1/14 (7.1%) local erythema.

We considered as suitable for conservative treatment those patients who had a reduction of the tumor size of 50% or more (PR and CR) according to the mammogram. In these patients we performed a partial resection of the breast (quadrantectomy, wide excision) with complete axillary lymphadenectomy. In case of SD or PD, a modified radical mastectomy (MRM) was carried out. In four cases of PR, we performed a MRM because of the desire of the patient and/or the small size of the breast, despite tumor reduction. We performed 7/14 (50%) MRMs, in one case with immediate breast reconstruction and 7/14 (50%) partial resections.

Histology showed 13/14 (92.9%) invasive primary carcinomas and 1/14 (7.1%) intraductal carcinoma; tumor grading was G1 in 5/14 (35.7%) patients, G2 in 5/14 (35.7%), and G3 in 4/14 (28.6%) cases. Node metastases were found in 9/14 (64.3%) patients.

A seroma occurred in one diabetic patient. No other postoperative complication was observed.

The median follow-up was 24.3 mo. All the patients are alive and up to now no one has shown local or distant relapse.

DISCUSSION

In recent years biological and clinical data suggested that drug treatment with cytotoxic chemotherapy can reduce the risk of relapse and mortality when given as adjuvant systemic therapy shortly after surgery for primary breast cancer [1]. Chemotherapy as a primary treatment in localized breast cancer has been advocated for a variety of theoretical reasons, based on both biological and clinical data [6].

Experimental systems suggest that noncurative reduction of tumor cell burden determines an increase of proliferation of residual tumor cells, because of the possible release of serum growth factors [7]. Clinical studies showed that early administration of cytotoxic drugs prevent an increase of metastatic tumor growth and prolong survival. Furthermore, the risk of generation and multiplication of resistant cells can be reduced by administrating chemotherapy as soon as possible, thus preventing further cell proliferation [8]. Some clinical data suggested that induction chemotherapy in locally advanced breast cancer may allow not only a reduction of tumor size, but also a better survival [9]. Therefore, several studies have been carried out in order to evaluate the effect of primary chemotherapy on local control of disease and on survival rates.

Neoadjuvant treatment has the potential advantages of

early treatment of systemic disease, reduction of tumor size before definitive local therapy, and allowing an assessment of the chemosensitivity of the primary tumor [10,11]. In several studies neoadjuvant chemotherapy has been shown to be effective in reduction of the primary tumor, thereby allowing conservative treatment in a large percentage of patients who where originally candidates for MRM [6,13]. However, many doubts and uncertainties (i.e., duration of the chemotherapy in relation to the response rate of the primary tumor, the best combination of drugs, effect on axillary status) should be resolved before neoadjuvant chemotherapy can be adopted as routine treatment [13]. In the same way, radiotherapy has been widely used as palliative treatment of locally advanced tumors [14] and as definitive therapy for stages I and II breast cancer, with very encouraging results [15].

Moreover, when primary radiotherapy was evaluated for reducing tumor size in order to allow conservative treatment, in large T2 and T3 lesions a global response was observed in >50% of the patients [16,17].

Recently, several studies have proposed the combination of radiotherapy and chemotherapy in the primary treatment of breast cancer [3,6,13]. The theoretical advantages of adding radiotherapy is that it may enhance chemotherapeutic efficacy by suppressing or reducing the proliferative activity of the subpopulations of cancer cells that survives chemotherapy in most cases [17]. Furthermore, a synergistic effect of chemotherapy and radiotherapy has been shown in a series of randomized clinical trials concerned with breast conservation [18].

In a study on primary chemotherapy in locally advanced breast cancer, it was shown that, although a cospicous percentage of neoplastic population was destroyed, the survived cells retained proliferative activity, which in some cases was more evident than the pretreatment one [19]. Integration of radiotherapy and chemotherapy could allow a control of this subpopulation [13].

Radiotherapy and chemotherapy have been integrated in several ways. Alternative administration seems to allow a full dose treatment, without increasing adverse effects and enhancing the therapeutic effects.

The main aim of this study was to evaluate the feasibility of the combination of chemotherapy and multifractionated accelerated radiotherapy in the treatment of patients who were candidates for radical surgery and the therapeutic effectiveness of such combination therapy. The percentage of responses that we observed was 78,6% (11/14: 1 CR and 10 PR). Only one patient showed a pancytopenia that required a short suspension of the treatment. No other major adverse effect was observed.

CONCLUSIONS

Despite the small number of cases, these results show the feasibility of this primary chemo-radiotherapy approach in the treatment of operable breast cancer. But to evaluate the impact of this kind of therapy on overall survival and risk of local recurrence and its possible introduction in the clinical practice, we need larger series and longer follow-up.

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